DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Division of Cardiovascular Devices
Pacing, Defibrillator & Leads Branch

Lead Review Memorandum

File: P010012/S026 (COMPANION)
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Summary

This panel-tracked PMA supplement is based upon the results from the COMPANION clinical trial (IDE# G990214) which evaluated optimal pharmacologic therapy (OPT), cardiac resynchronization therapy (CRT-P), and cardiac resynchronization therapy with defibrillation (CRT-D) in subjects with moderate to severe heart failure. This submission is limited to the sponsor's CRT-D devices and seeks the following:

?? Modifications to the Indications for Use statement to specify a mortality benefit and to indicate the device for the entire population studied in the COMPANION trial.
?? Modifications to the Clinical Studies section of the labeling to include results from the COMPANION trial.

All devices under review for this submission are currently market-approved.

Indications for Use

The sponsor's approved Indications for Use statement currently reads as follows:

> *Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are intended to provide ventricular antitachycardia pacing and ventricular defibrillation for automated treatment of life threatening ventricular arrhythmias. Guidant CRT-Ds are also indicated for reduction of symptoms of moderate to severe heart failure (NYHA III/IV) in patients who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF</= 35%) and QRS duration >/= 120 ms.*

The sponsor is seeking the following Indications for Use statement:

> *Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) are indicated for patients with moderate to severe heart failure (NYHA III/IV) who remain symptomatic despite stable, optimal heart failure drug therapy, and have left ventricular dysfunction (EF </= 35%) and QRS duration >/= 120 ms.*
>
> *Guidant Cardiac Resynchronization Therapy Defibrillators (CRT-Ds) have demonstrated the following outcomes in the indicated population specified above:*
>
> - *Reduction in risk of all-cause mortality or first all-cause hospitalization*
>
> *Note: Hospitalization is defined as administration of IV inotropes or vasoactive drugs > 4 hours (outpatient or inpatient), or admission to a hospital that includes or extends beyond a calendar date change.*
>
> - *Reduction in risk of all-cause mortality*
> - *Reduction of heart failure symptoms*

Devices under Review

The sponsor is seeking approval for the above Indications for Use statement for all of its commercially available CRT-D models. These include CONTAK CD Model 1823; CONTAK CD 2 Models H115 and H119; RENEWAL Model H135; and RENEWAL 3 Models H170, H175, H177 and H179. Only the CONTAK CD device, however, was used in CRT-D arm of the COMPANION trial. In previous submissions to FDA (P010012/S002, approved 12/20/2002, and P010012/S008, approved 6/13/2003), the sponsor demonstrated the applicability of available CONTAK CD clinical data to its RENEWAL devices. Future CRT-D models, however, will also require this type of justification to demonstrate that results from COMPANION still apply.

COMPANION Clinical Trial Design

The trial design is described in detail in the clinical review but is briefly described here. The COMPANION trial was a three-arm study designed to demonstrate the benefits of cardiac resynchronization therapy, with or without a defibrillator in the treatment of patients with moderate to severe heart failure.

Important entry criteria for the trial were:

- ?? Moderate or severe heart failure (NYHA class III or IV)
- ?? QRS duration = 120 ms
- ?? Left ventricular ejection fraction = 35%
- ?? Left ventricular end diastolic dimension = 60 mm
- ?? Age = 18 years
- ?? On optimal pharmacologic therapy for heart failure
- ?? Not indicated for a pacemaker or ICD

The endpoints of the trial were:

- ?? All-cause mortality plus all-cause hospitalization (primary)
- ?? Total survival (secondary)
- ?? Cardiac morbidity (secondary)
- ?? Exercise performance (sub-study)

Patients were randomly assigned to OPT, OPT with CRT-P, or OPT with CRT-D, with a patient ratio of 1:2:2 respectively. The hypotheses compared outcomes for both CRT-D and CRT-P arms with the control (OPT) arm. The first contrast (CRT-D vs. OPT) was allocated 0.03 of alpha and the second contrast (CRT vs. OPT) was allocated 0.02 of alpha.

The study was initially planned to enroll 2200 patients but was stopped (1638 patients enrolled) by the Data Safety and Monitoring Board after it was predicted that the primary and secondary (mortality) endpoints had been met for the CRT-D arm of the trial. At that point in time, enrollment had essentially ceased due to the fact that CRT devices had become available to patients not enrolled in the trial.

Exercise Sub-study
A subset of the patients participating in the COMPANION trial was selected to participate in the Exercise Performance Sub-study. The co-primary endpoint for this sub-study consisted of Peak VO_2 derived from a symptom-limited exercise test and six-minute hall-walk distance. Additional secondary measurements included Quality of Life as measured by the Minnesota Living with Heart Failure Questionnaire and NYHA Class. CRT results were pooled from the CRT-P and CRT-D arms to compare CRT to OPT.

Results from the Exercise Performance Sub-study were reviewed by FDA as part of the approval submissions for the sponsor's CRT-D and CRT-P devices (P010012 and P030005, respectively). Therefore, these data were not reviewed in detail as part of this submission.

Statistical Plan
The sponsor and FDA agreed to the statistical plan described in the COMPANION protocol (Investigational Plan, Appendix B) which allocated 0.05 of alpha to each of the four endpoints described above. The sponsor addresses the multiplicity issue this plan presents by stating that they will "…be conservative in the interpretation of the multiple analyses, looking for consistency across variables." Under this plan, no one endpoint may be considered in isolation. Therefore, in order to assess the impact of the CRT-D device on mortality, FDA must also assess its impact on the other endpoints of the trial.

COMPANION Regulatory History
The regulatory history of the COMPANION clinical trial is extensive and includes the following important events:

- **June 16, 1999**- COMPANION pre-IDE meeting to discuss planning of the trial.
- **August 4, 1999**- COMPANION IDE agreement meeting.
- **September 2, 1999**- COMPANION IDE submitted to FDA.
- **September 8, 1999**- Agreement Letter sent from FDA[1]. This letter confirmed FDA and Guidant's concurrence regarding the primary and secondary endpoints of the trial and the claims each would support. The letter also referenced the statistical plan for how the trial results would be evaluated. Importantly, the trial was not designed to assign significance to comparisons between the CRT-P and CRT-D arms. Only descriptive statistics would be performed for these comparisons.
- **October 1, 1999**- COMPANION IDE conditionally approved by FDA.
- **January 20, 2000**- First patient enrolled in COMPANION trial.
- **January 26, 2000**- First device implant in the trial. Enrollment steadily increased over the next 1.5 years to a peak of approximately 105 patients per month.
- **June 16, 2000**- COMPANION protocol revised primarily to modify the inclusion/exclusion criteria related to the definition of moderate or severe heart failure and to add the new EASYTRAK model and associated devices.

[1] Agreement decisions are binding on both FDA and the sponsor. They can be changed only with the written agreement from both parties or when there is a substantial scientific issue essential to determining the safety or effectiveness of the device.

?? **July 14, 2000**- Number of COMPANION centers increased from 80 to 130.
?? **May 17, 2001**- COMPANION protocol revised to include EASYTRAK implant recommendations from the Steering Committee and new definitions for coronary sinus trauma. Instructions regarding the exercise sub-study were modified as well.
?? **July 10, 2001**- FDA panel meeting to review device approval submissions for InSync and CONTAK CD devices.
?? **August 28, 2001**- First CRT device approved (InSync). At this point, enrollment in the COMPANION trial began to decline, presumably due to the fact that a CRT device had become available to patients with heart failure.
?? **November 20, 2001**- MADIT II trial stopped.
?? **March 19, 2002**- MADIT II results published in New England Journal of Medicine.
?? **May 2, 2002-** First CRT-D device approval (CONTAK CD). By this point in time, enrollment in the COMPANION trial had declined to less than 30 patients per month.
?? **May 28, 2002**- COMPANION protocol revised primarily to expand the trial from 130 to 145 investigational sites and to modify the procedure for switching OPT patients to CRT therapy based on the commercial availability of CRT devices for the COMPANION population.
?? **June 26, 2002**- InSync ICD received FDA approval, beginning a steeper decline in enrollment rate.
?? **July 18, 2002**- MADIT II expanded ICD indication approved.
?? **November 1, 2002**- Meeting between FDA and Guidant to discuss revision to the CONTAK TR agreement to modify the endpoint for device approval.
?? **November 14, 2002**- Revised agreements letter sent from FDA.
?? **November 20, 2002**- DSMB recommended that the COMPANION trial be stopped.
?? **December 17, 2002**- IDE supplement submitted to reduce patient follow-up and incorporate DSMB recommendations
?? **February 28, 2003**- COMPANION protocol revised to reduce follow-up evaluations and incorporate Steering Committee recommendations to: (1) recommend that patients randomized to OPT receive a CRT device based on the preliminary results of the trial and individual patient considerations and (2) recommend that patients randomized to a CRT-P be considered on an individual basis for a commercially available CRT-D device.
?? **March 21, 2003**- Original PMA submitted for CONTAK TR/RENEWAL TR.
?? **December 24, 2003**- PMA supplement submitted seeking expanded indications and mortality benefit claims for Guidant's CRT-D devices based on exercise performance and mortality data from COMPANION.
?? **January 26, 2004**- CONTAK TR/RENEWAL TR PMA approved.
?? **February 11, 2004**- December 24th submission withdrawn.
?? **March 17, 2004**- Teleconference between FDA and Guidant to discuss dataset to be included in the upcoming submission. At this meeting, it was agreed that the data would be submitted in two parts. The initial dataset would be submitted by March 26, 2004, and would include mortality, exercise performance and adverse

event data for the CRT and OPT arms. The second dataset would be submitted by April 15, 2004 and would include the primary endpoint analysis and all-cause hospitalization data. All-cause hospitalization data was intended to replace the not yet completed cardiac morbidity endpoint. It had not yet been determined whether or not data from the CRT-P arm would be included in this submission.

- ?? **March 26, 2004**- PMA supplement (P010012/S026) submitted seeking expanded indications and mortality benefit claims for Guidant's CRT-D devices. The first of two datasets described above was included in this submission.
- ?? **March 29, 2004**- Filing date for P010012/S026. FDA concluded that the submission qualified for expedited review.
- ?? **April 1, 2004**- Meeting between FDA and Guidant to discuss the CRT-P data to be included in the second part of the submission. It was agreed that CRT-P data was integral to the review of the CRT-D device and would be included in this submission.
- ?? **April 15, 2004**- Second part of P010012/S026 submitted to FDA. This dataset included the primary endpoint analysis and all-cause hospitalization data. All endpoint data related to the CRT-P arm was also included.
- ?? **May 20, 2004**- COMPANION results published in the New England Journal of Medicine.
- ?? **June 25, 2004**- The sponsor requested to modify the proposed Indications for Use statement to be discussed at panel meeting. The updated statement is included in this review. The clinical and statistical reviews were conducted based on the statement that was originally submitted by the sponsor.

Overall Review Concerns

In order to meet the expedited schedule, FDA has maintained a high level of interaction with the sponsor during the course of the review. Rather than submit a formal list of deficiencies to the sponsor, FDA submitted a series of informal requests and questions through email and teleconference as they arose from our review. The sponsor responded in kind, submitting data informally for more rapid review, and later formally submitting data, responses, and minutes from each teleconference. Specific clinical and statistical issues are discussed in those consulting reviews. However, some major concerns were raised which required lengthy discussion between the sponsor and the entire FDA review team. These concerns are discussed here as well as in the consulting reviews.

Changes to Hospitalization Definition for Primary Endpoint Analysis

The COMPANION clinical protocol defined the primary endpoint as the time to the first event of either all-cause mortality or all-cause hospitalization where:

> "…all-cause hospitalization is defined as admission to a hospital for any reason. In addition, this endpoint will include emergency room visits (or unscheduled office visits) that result in treatment with intravenous inotropes or vasoactive drugs."

However, the definition of hospitalization that was used in the analysis for this submission was:

> "…hospitalizations for any reason that required the patient to be in the hospital for a period of time in which there was a calendar date change or outpatient infusions of intravenous vasoactive or inotropic therapy exceeding four hours."

On May 10, 2004, FDA requested clarification from the sponsor as to why and when the hospitalization definition was changed, thus beginning a series of conversations between FDA, the sponsor, and Dr. Peter Carson, chair of the Mortality and Morbidity (M & M) Committee for COMPANION, regarding this issue.

Based on these conversations, it is FDA's understanding that the M & M committee viewed the definition of hospitalization as having not been clearly established in the protocol. Therefore, prior to the first committee meeting on March 16, 2001, the M & M committee established a new definition for hospitalization which only included hospitalizations greater than 24 hours or emergency room treatment with intravenous inotropes or vasoactive drugs administered for greater than four hours. Using this definition, the committee adjudicated 150 events including 113 hospitalizations. During this time, it was concluded that the precise time of hospital admission and discharge was difficult to ascertain. Therefore prior to its January 19-20, 2002 meeting, the committee modified the hospitalization definition again, this time to require a calendar date change rather than an in-patient duration of 24 hours. Analysis was performed retrospectively to classify all hospitalizations according to the new criteria.

It is FDA's understanding that a sufficiently complete dataset of in-patient hospitalizations not resulting in a calendar date change is not available since investigators were not clearly instructed to record that data. As a result, it is not possible to recalculate the primary endpoint based on the original definition of a hospitalization. Therefore, FDA has evaluated the primary endpoint based on the definition provided in this submission. FDA is concerned that changing the definition of the primary endpoint midway through the trial may raise concerns regarding the interpretability of the results. These concerns are described in detail in the clinical consult. FDA requests that the advisory panel provide guidance as to how best to interpret this modified endpoint.

Data Obtained from Patients after Withdraw Used in Primary and Secondary Analyses
During the course of the COMPANION trial, the InSync and CONTAK CD devices were approved for use in large portions of the COMPANION population. With CRT available to patients as a medical option, some patients in the OPT arm of the trial received device implants. In an effort to preserve the relevance of the OPT arm data, Guidant modified the protocol on May 28, 2002 to limit the number of device implants in OPT patients by placing the following restrictions on investigators:

> "To minimize confounding, patients in the optimal pharmacologic therapy arm who develop an indication for a conventional pacemaker or ICD may receive a device with biventricular pacing capability or biventricular pacing with ICD back

up capability only if the patient has been hospitalized for decompensated heart failure or meets class I indications for ICD implantation. The case must be presented to and approved by the Steering Committee prior to implantation. Switching patients from the optimal pharmacological therapy arm to biventricular therapy without consulting the steering committee will result in a class 1 deviation."

As a result, an unanticipated and substantial number of patients withdrew from the OPT arm of the COMPANION trial in order to receive a commercially available CRT, CRT-D, or ICD device. The differential withdrawal rate occurred in 26%, 6% and 7% of patients in the OPT, CRT and CRT-D groups, respectively. To mitigate the withdrawal rate, the independent statistical group recommended and the Steering Committee implemented a policy of approaching withdrawn patients, or their families, to sign a consent allowing collection of data related to vital status, device status and hospitalizations occurring prior to December 1, 2002. Data from patients who withdrew from the trial but who were determined to have not withdrawn their consent were used without re-consenting those patients.

The contract research organization identified 128 patients at 61 centers who were withdrawn from the trial. COMPANION research coordinators at each site were sent a listing of patients at their site who withdrew without experiencing a primary endpoint prior to December 1, 2002. They were advised to complete re-consenting for those patients who had withdrawn their consent. In addition, they were advised to collect any information on hospitalizations using a standardized form. They were also advised to complete a hospitalization case report form and provide any available source documentation to allow for adjudication of the primary endpoint event.

Data obtained from patients withdrawn from the study was used to modify the calculation of the primary endpoint and the secondary endpoint of mortality. The algorithm for doing so was explained in Amendment 3, submitted May 17, 2004, in answer to FDA's questions on this point. In an effort to evaluate the results of the trial as originally specified in the protocol, FDA analyzed the primary endpoint as well as all adverse event and hospitalization data by censoring the dataset for withdrawn patients at the time of withdraw. Due to time constraints, mortality was analyzed using all of the data submitted by the sponsor. This issue is discussed further in the clinical and statistical reviews. FDA requests guidance from the panel in determining whether data from patients after withdraw should be used in the results presented in the device labeling.

Characterization of Adverse Events and Hospitalizations

As is thoroughly described in the clinical review, analysis of the COMPANION data revealed an increase in adverse events in the CRT-D arm compared to OPT. Patients in the CRT-D arm also experienced more hospitalizations and spent more days in the hospital when implant hospitalizations were included. While there were no pre-specified endpoints to evaluate these parameters, they are nonetheless meaningful to patients and physicians. FDA requests guidance from the panel in determining how adverse events and hospitalizations should be characterized in the device labeling.

Consulting Reviews
Please refer to the detailed clinical and statistical reviews performed by Dr. Proestel and Dr. Krasnicka, respectively.

A second clinical review was performed by Dr. Ileana Piña. Dr. Piña concurred with all of Dr. Proestel's analyses. In addition, Dr. Piña concluded that beta blocker dosages evaluated at baseline, 6 months, and 12 months for both the CRT-D and OPT patients in COMPANION were substantially lower than that of similar patients in the MERIT HF and COPERNICUS clinical trials.